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**Trading participation for access to health-care:
A morally relevant feature of participation in clinical research**

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Abstract

The increasing tendency to run clinical trials offshore in low- and middle-income countries (LMICs) has been extensively documented. In parallel, in high-income countries (HICs) as the US, we are witnessing the emergence of new forms of clinical research where un(der)insured fractions of the population are trading access for participation to health-care to which they would otherwise not have access.

We first discuss Wertheimer's analysis of offshored clinical trials as mutually advantageous exploitative transactions. We then argue that to make sense of what is morally problematic with the offshoring of clinical research it is necessary to broaden the ethical analysis, as there are different kinds of moral wrongs that can be linked to exploitation. We then further broaden our gaze beyond exploitation to analyse a distinct sort of moral wrong inherent in the off-shoring of clinical research, namely the sponsors' complicity in perpetuating the injustice of the background conditions of the participants.

We argue that both modes of participation in clinical research highlighted above share the feature of 'trading participation for access to health-care', and that this is a morally relevant characteristic that should be taken into consideration in the ethical

analysis, and that in some cases justify intervention to prevent subjects from participating in clinical trials.

We conclude that as health-care provision and clinical trial participation have been and continue to be strictly intertwined both in LMICs and in HICs, in both contexts, there is a need to devise ways to make the inclusion of economically disadvantaged and uninsured individuals in clinical research as fair as possible.

1. INTRODUCTION

An ethics of human subject research that does not account for the general lack of access to health-care is dangerously limited, and pharmaceutical clinical trials cannot be ethical until social inequalities are recognized, and more expansive measures aimed at mitigating social inequalities are devised (Fisher 2008, 215).

The increasing tendency to run clinical trials offshore in low- and middle-income countries (LMICs) has been extensively documented (Petryna, Lakoff and Kleinman 2006; Petryna 2009). Recently, Robert Califf, Vice Chancellor for Clinical Research at Duke University, reported to the U.S. Presidential Commission for the Study of Bioethical Issues that a massive shift has occurred over the last decade to middle-income countries such as India, China, South America, and to low-income countries in sub-Saharan Africa (Donnelly 2011). In parallel, in the US, we are witnessing the emergence of new forms of clinical research where un(der)insured fractions of the population are trading access for participation to health-care to which they would otherwise not have access (Elliott 2008; Abadie 2010).

What do these different modes of participation have in common? Moreover, why are they ethically problematic? In this paper, we argue that they share the morally relevant feature of ‘trading participation for access to health-care’, and that this is a morally relevant feature that should be taken into consideration when evaluating the justifiability of both modes of participation in clinical research.

2. ENCOURAGING MUTUALLY ADVANTAGEOUS EXPLOITATIONS

Are clinical trials offshored to LMICs exploitative? If they are, does this imply that we should intervene to prevent them from taking place? These two questions need to be

distinguished. In this section, we discuss the concept of exploitation through Wertheimer's lens (2010), before moving on to the analysis of broader accounts of exploitation in section 3. According to Wertheimer, the moral wrong identified with exploitation is one of the unfairness of the distribution of the resources created through interaction, but what is often not clear in the discussions about the ethics of exploitation is what kind of distribution would count as fair and why.

Wertheimer (2010) further classifies transactions between individuals as being (a) consensual or (b) non-consensual. He also classifies such transactions as being (i) mutually advantageous or (ii) non-advantageous (neutral or harmful) for at least one of the two parties. These distinctions cross-cut each other. According to Wertheimer (2010), clinical trials offshored to LMICs can be considered as an instance of a *mutually beneficial* transaction, defined as a transaction in which both the pharmaceutical companies and the subjects benefit from it: the former because of the information they obtain through the trial, while the latter because they get access to health-care resources that would not otherwise be available to them.

The premise itself on which Wertheimer bases his reasoning (i.e. that it offshored clinical trials can be considered mutually advantageous transactions) is problematic. Indeed, it is not necessarily the case that short-term benefits such as access to health-care for the duration of the trial will leave the subjects better off in the long run than no access to health-care at all, as for example the trial may have exposed them to risks that will reverberate in the future when the participants have no access to the limited health-care provided by the trial anymore. Suppose though for the sake of the argument that off-shored clinical trials could indeed be considered mutually advantageous transactions for both pharmaceutical companies and subjects. We will then argue that, even on the basis of this strong premise, there are moral reasons that justify intervening in some circumstances to prevent such trials from taking place. It is obvious therefore that our conclusions will gain even more traction if we challenged the premise that off-shored clinical trials are mutually advantageous transactions.

Wertheimer argues that we should not interfere with the offshoring of clinical trials, and grounds his arguments in what he calls the Principle of Permitting Exploitation (hence, PPE), defined as 'the claim that it would be wrong to interfere with such [mutually beneficial consensual] transactions' (Wertheimer 2010, 218). Then, he draws a distinction between the moral desirability of interfering with particular

transactions, and the moral desirability of the transactions themselves, and argues that the PPE is only a claim about *the ethics of interference* [emphasis added], and not a claim about the ethics of a transaction itself. In the example he provides of the Surfaxin trial, (Charatan 2001) given the reality of the economical and geographical situation of LMICs in which the trial was outsourced (Bolivia, Chile, Ecuador, and Mexico), for Wertheimer it was a rational choice for caregivers to decide to enrol their children in Surfaxin trial, where they had a 50 % chance of receiving an active treatment (surfactant) and a 50 % chance of receiving a placebo. To the contrary, he argues that the same choice would be irrational for US citizens (or other citizens in HICs) who (provided that they are well-insured or have access to a well-functioning public health system) already have access to the best available therapy (Wertheimer 2010, p 252). A similar kind of narrative is employed to describe the participation in clinical trials in the US for those un(der)insured fractions of the population for which participation is the only way to access health-care. As put by Fisher:

By privileging the individual and choice, a health care system mediated by neoliberal policies and cultural sensibilities tends to obscure the inequalities to which those who participate in clinical trials tend to be subject. Within this frame, the systematic use of uninsured or economically disenfranchised people as human subjects in pharmaceutical studies is not seen as being exploitative but is instead positioned as an opportunity for members of those groups (Fisher 2008, p 17).

We think that such kind of narratives are extremely problematic, as subjects participating in Phase 1 trials in the US are ‘choosing’ to do so to get access to health-care resources they would otherwise not have access, as documented by Fisher. As we will argue below, this ‘trading participation for access to health-care’ feature of participation in clinical research is a morally relevant feature that we should consider when evaluating the ethical permissibility both of offshored clinical trials to LMICs and to clinical trials recruiting health subjects from economically disadvantaged fractions of the populations in the US. Not only does Wertheimer argue that we should not prevent the offshoring of clinical trials, but he adds that ‘we should *positively enable* [emphasis added] transactions that are beneficial to the disadvantaged and to which they consent’ (Wertheimer 2010, p 222) and that: ‘[...] *it clearly would be unfair* [emphasis added] to exclude prospective research subjects facing background injustice, such as lack of health insurance, who are attempting to advance their interests via research participation

simply because their background conditions are unfair' (Wertheimer 2010, pp 106-7). Therefore, we think that his 'PPE' could be better referred to as the 'Principle of Encouraging Exploitation' or 'PEP'.

However, is it the case when it "clearly" would be unfair to exclude prospective research subjects from participation in research? As we argue in the next section, there is more to the account of exploitation than an analysis of mutually advantageous transactions, and in some cases, it would *not only not be unfair* to exclude prospective research subjects from participation, but that it would also be a moral duty to do so.

3. A MORE COMPREHENSIVE ACCOUNT OF EXPLOITATION

How we frame the issue of offshoring clinical research is not just a question of theoretical accuracy, but it also has important practical implications. In order to make sense of what is morally problematic with the offshoring of clinical research, it is necessary to broaden the ethical analysis of offshored clinical research beyond exploitation. We will do this in two steps: in this section we will argue, following Snyder (2012), that there are different kinds of moral wrongs that can be linked to the charge of exploitation, and that Wertheimer's account of exploitation is unjustifiably limited. In the next section, we will further broaden our gaze to analyse a distinct sort of moral wrong inherent in the offshoring of clinical research, namely the sponsors' complicity in perpetuating the injustice of the background conditions of the participants. As mentioned before, what is often not clear in the discussions about the ethics of exploitation is what kind of distribution would count as fair and why.

To fill this gap in the bioethical discourse, Snyder (2012) proposes two accounts of exploitation as fairness. He refers to the first one as the 'microfairness' account. In this account, the range of contextual factors that will determine whether a distribution of resources counts as unfair or not is limited to the risks and benefits of the transaction. This view excludes all the external factors such as global economic structures, past and present injustices against individuals, and the socioeconomic position of the various actors. (Snyder 2012, p 253) This 'microfairness' level, we add, is the one referred to by Wertheimer. The second, broader level of analysis spelled out by Snyder is the 'macrofairness' level, which takes into account the background conditions, the existing structural inequalities, and injustices when determining whether the distribution of

resources resulting from an interaction is fair. Both levels need to be taken into account when evaluating the ethical permissibility of a transaction. In addition, Snyder identifies another level that we need to acknowledge to understand the ways in which a transaction with particular other persons can create new demands on the persons involved in the transaction: this is the level of exploitation understood in the Kantian way as ‘mere use of others.’ Snyder’s comprehensive account of exploitation incorporates these three levels to account for the moral intuition that it can be wrong to press one’s advantage or to take full advantage of others’ vulnerabilities in certain settings.

It is in this last sense of exploitation as mere use of others that by failing to provide pharmacologically active treatment in the control arm of the trial (as in placebo-controlled trials as the Surfaxin trial) or to secure access to the benefits of the trial that the researcher or sponsor may fail to discharge a duty of beneficence. Note that the duty of beneficence is understood typically as an imperfect duty, giving the agent (researchers/sponsors) latitude as to when, how and to whom it will be discharged. (Sofaer 2013) The moral concern here is that treating exploitation as the violation of an imperfect duty only fails to acknowledge the ways in which a relationship with particular other persons can create new demands on our resources. Exploitation is typically criticized as disregarding the needs of a particular person, while an imperfect duty of beneficence allows the researcher to fully discharge her duty to attend to the needs of others by helping any person in need anywhere in the world.

To recapitulate, the microfairness level establishes that localized asymmetries in the bargaining position of actors can create a vulnerability that if fully or even partially taken advantage of, allows the better-positioned party to secure much more of the social surplus created by the interaction than it would be in a more competitive, better balanced or more equal relationship. Exploitation understood as macrofairness describes how background institutions can create long-term asymmetries in the bargaining power of actors, and the offshoring of clinical research can perpetuate/exacerbate the unfairness of the background conditions. Finally, exploitation as the mere use of others shows that we can fail to meet our specified obligation of beneficence toward others, and harness resources that are owed to others for our use.

The three forms of exploitations outlined by Snyder can coexist or not in the same transaction, and consequently, their analysis is relevant to the discussion of the

ethical permissibility of the transaction. An account of exploitation such as Wertheimer's that excludes all the contextual and macro-economical factors of participation seem to us to be unjustifiably limited, and too lenient on the pharmaceutical sponsors.

4. NOT ONLY EXPLOITATION: COMPLICITY IN PERPETUATING INJUSTICES

Exploitation is only part of what makes offshoring clinical trials ethically wrongful. A distinct sort of moral wrong intrinsic in the offshoring of clinical research is what is referred to by Malmqvist (2013) as 'complicity in injustice'. Malmqvist argues that the moral wrongness of offshoring clinical research resides in the circumstances from which the exchanges arise, i.e., the background conditions of the participants, which are not merely unfortunate, but also deeply unjust. Pharmaceutical companies ('A') use subjects' ('B') unjust circumstances to get B to agree to transact on terms that B would not have accepted under different/more just circumstances. While voluntary (consensual) and mutually beneficial (advantageous), their exchange would not have occurred or would have benefited (B) more or (A) less, the background conditions of the subjects had been different. In other words, A takes advantage of injustice. In addition, another shortcoming in an account of offshoring clinical research limited to exploitation only is that the focus of the analysis treats clinical trials as if they were transactions among two parties, whereas in reality they often involve more than two actors. As pointed out by Mitra (2013), in offshored clinical trials, the transaction might be better illustrated by 'B as a participant and A as a long chain of actors standing in different relationships to each other and to B' (Malmqvist 2013, p 113). The point here is that A represents a group of people, with varying and 'sometimes conflicting professional obligations, most of whom have a more powerful bargaining position than B' (Malmqvist 2013, p 114).

Hence, what exactly is morally wrong with turning other people's unjust circumstances into profit for oneself? Malmqvist argues it is not strictly speaking a matter of exploitation, but of becoming implicated in the perpetuation of structural injustices: 'Only from the standpoint of complicity can we see why it matters that it is

an unjust, rather than a tough but fair, situation that is taken advantage of” (Malmqvist 2013, p 115).

We do not wish to dwell here on the causal relations of complicity but highlight the upshot of Malmqvist’s argument, namely that many offshored clinical trials benefit third parties (i.e., affluent countries), and give them reasons /incentives not to change the status quo of LMICs. To put it simply, they perpetuate injustices.

The question of who has the duty to repair B’s unjust circumstances remains open. As pointed out by Sofaer (2013), there is a widespread lack of clarity among research agents, research ethics committees and host communities ‘about who owes what to whom, and why’ (Sofaer 2013, p 113). The principle(s) of reciprocity seek to address apparent imbalances in the distribution of costs and benefits in off-shoring of clinical research, but although there is a great variety of reciprocity principles in the post-trial access (PTA) literature, (i.e. literature discussing whether research participants should have PTA to the trial drug), as shown by Sofaer, these principles are very difficult to justify and the most plausible instance of the principle, the Net Instance (which applies only to persons who bear substantial risk through participating in clinical research), could be justified only in the context of research on the basis of the ‘research exceptionalism’ view put forward by Wilson and Hunter that ‘research merits stringent regulation despite the fact that it is no riskier than many other activities which we do not regulate stringently’ (Sofaer 2013, p 113). In the next section, we attempt to spell out on different grounds from reciprocity principles why we may, in fact, be justified in interfering with what we assumed at the beginning of the paper to be mutually advantageous transactions.

5. IS IT EVER ETHICALLY JUSTIFIED TO INTERFERE WITH MUTUALLY ADVANTAGEOUS TRANSACTIONS?

As we have seen above, one of the commonly used rhetoric of participation is that by being participants we are reciprocating the benefits that we receive as patients, or as put by Mitra (2013), as an ‘indirect form of participation’, where ‘researchers and participants both contribute to the health system (Sofaer 2013, p 115). Some have also argued for a duty to participate in research. However, as pointed out by De Melo Martin (2008), the context of research is essential for making any such kinds of claims. For

example, can we argue that subjects should have a duty to participate in trials that they are not enjoying the benefits of, or that subjects should have a duty to participate in trials when their level of access to medicines and biomedical technologies is so low, if not non-existing? In addition, as pointed out by Sofaer (2013), most if not all reciprocity-based principles fail. Therefore, it seems to us that we need to find a different ground on which to redress the inequalities in the distribution of risks and benefits in off-shored clinical research than a duty to participate in research based on the principle of reciprocity.

We have argued elsewhere that the context of clinical research, and the unfairness of the background conditions of prospective subjects, needs to be taken into account when evaluating the ethical justifiability of a trial. [reference omitted for peer review] By context we refer to the background conditions of the participants, and the availability of other options to access health-care when deciding whether to enrol or not in research. The background conditions to participation reduce or cancel out the options available to the subjects to have access to treatment outside of the trial. This is what we refer to as the ‘trading participation for access health-care’ characteristic of the trial, and we think it is a morally relevant feature that needs to be taken into account in the overall ethical evaluation of the trial. Note that the ‘trading participation for access to health-care’ feature of the trial is not a unique feature of clinical trials performed in LMICs. On the contrary, as mentioned above, the ‘trading participation for access to health-care’ feature that defines many clinical trials offshored to LMICs can be found also in many other social disadvantaged conditions of the participant in HICs (for one, the US) for the large portions of the population who are uninsured or under-insured, and are motivated to enrol in clinical trials as they perceive them as their only option to receive a medical care to which they would otherwise not have access. The current narrative of participation in clinical trials is that it is rational for those fractions of populations to participate in clinical trials. A very similar kind of narrative is employed for the participants in clinical trials in LMICs, for whom it is said that it is rational to choose it and to engage in a mutually advantageous transaction, and as argued by Werthimer, that it would be ‘unfair’ to exclude them from participation. Even on the problematic premise that offshored clinical trials can be understood as mutually advantageous transaction, we argue that both kinds of participation in clinical research remain wrongful, as the stronger party is taking advantage of the limited or non-existing

options of the participant to have access to health-care, and by doing so is perpetuating the injustice of the background condition of the subject.

Furthermore, we argue that, if it is the case that a trial represents an instance of wrongful exploitation, insofar as the pharmaceutical company is taking advantage of the fact that the participants have no other way to access health-care or treatment outside of participation in the trial, then we have moral reasons grounded in a broader understanding of the concept of exploitation not limited to the ‘microfairness’ of the transaction, and in Malmqvist (2013) complicity in injustice arguments, to intervene to prevent such trials from taking place.

We recognize that this is a not an easy stance to take for at least the following two reasons: a) the desired effects of intervening to prevent the mutually advantageous transactions from taking place are likely to be more distant and uncertain than the effects brought about by the mutually advantageous transactions; b) we need to be honest about the fact that interfering with the mutually advantageous transactions may harm the participants by depriving them of the possibility to get access to (a very limited) health-care that they would otherwise not have access to. However, even though we seriously want to take into account the above factors, we think that ‘it isn’t always unreasonable to prioritize large-scale social change over individual interests’ (Sofaer 2013, p 123) (note that we are still reasoning on Wertheimer’s premise that offshored clinical trials are mutually advantageous transactions).

In addition, another point demands attention, i.e., the possibility that preventing the clinical trials to take place may harm the participants in the short-term, but benefit them in the long-term, by contributing the redress the social injustices of the background conditions of the participants. As said above, the offshoring of clinical research to LMICs or the outsourcing of clinical trials to pharmaceutical companies recruiting subjects as participants from economically disadvantaged fractions contributes to perpetuating the status quo and exacerbate the social inequalities. As noted by Malmqvist though, ‘The complicity argument may look more utopian [than Wertheimer’s mutually advantageous understanding of clinical research] because the desired effects are likely to be more distant and uncertain’ (Malmqvist 2013, p 23).

What it seems important to us to preserve in Wertheimer’s account of offshored clinical research is his real-world ethical analysis. We do not live in an idealized world

where idealized standards of fairness reign, and we also think, as Wertheimer does, that an idealized, a contextual way of doing bioethics would not only be useless but at times plainly pernicious. Hence, it is important that we remain grounded in a contextual analysis of the real-world conditions of the transactions. In other words, we agree with Wertheimer that arguing for a universal standard of fairness, and on the basis of this standard prohibiting mutually advantageous transactions in LMICs, would simply leave people worse off than they currently are. This does not mean, though, that we should not aim for incremental changes, and limit our analysis only to the microfairness level of the transaction as Wertheimer does. On the contrary, we should aim at small incremental changes towards a better world on the basis of an ethical analysis that takes into account the real-world conditions. The best that we can reasonably hope for is a mitigation of the unfair conditions of the subjects by ensuring PTA to drugs, and small steps towards a different model in the long run, by acting to prevent some of the most unfair offshored clinical trials from taking place. This can happen only at the expense of some subjects getting access to limited health-care for the duration of a trial. The question of how to enforce this prevention is completely a separate question that we cannot address in this paper, nor have we the skills to do so.

6. CONCLUSIONS

In this paper, we argued that Wertheimer's account of offshored clinical research is unjustifiably limited and that in order to capture all the nuances of the moral wrongs associated with offshored clinical trials a broader ethical analysis, not limited to an analysis of exploitation, but that includes contextual factors in clinical trial participation. In addition, we argued that the fact that sponsors are taking advantage of the unfairness of the background conditions of the subjects is *de facto* equivalent to becoming complicit in injustice. The background conditions to participation in clinical research reduce or cancel out the options available to the subjects to have access to treatment outside of the trial. This is what we refer to as the 'trading participation for access health-care' characteristic of the trial, and we think it is a morally relevant feature that needs to be taken into account in the overall ethical evaluation of the trial. This is not a unique feature of clinical trials performed in LMICs. Although health-care provision and clinical trial participation have historically been considered separate issues, they have been and continue to be strictly intertwined, both in LMICs and in

HICs, as in both contexts there is need to devise ways to make the inclusion of economically disadvantaged and uninsured individuals in clinical research as fair as possible, while remaining grounded in a real-world ethical analysis.

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